## REMARKS

These remarks are in response to Office Action dated January 30, 2007. Claims 1, 5 and 11 have been amended. Claims 2 and 4 have been cancelled without prejudice. Claims 7 and 14 have been withdrawn from consideration. Subsequent to the entry of the present amendment, claims 1, 3, 5-6, 8-13, and 15 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

### Claim Objections

Applicants respectfully traverse the Examiner's objections regarding claim 2 arising from the alleged informalities. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have cancelled claim 2 rendering the objection moot as to the claim. Withdrawal of the objection is respectfully requested.

### Rejections under 35 U.S.C. §112, First Paragraph (written description)

Applicant's respectfully traverse the rejection of claims 1-6 and 8-10 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Office Action alleges that because the specification and claims do not set forth structure encompassed by the claims they fail the written description requirement. Applicants respectfully submit that the rejection is moot with regard to the claims because claims 2 and 4, which relate to claiming structural aspects of method inhibitors, have been canceled.

Applicants respectfully request withdrawal of the rejection.

### Rejections under 35 U.S.C. §112, Second Paragraph

Applicant's respectfully traverse the rejection of claims 1-4 under 35 U.S.C. §112, second paragraph as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action

alleges that claim 1 fails to recite requisite steps necessary to practice the invention. Applicants respectfully traverse the rejection as it applies to the pending claims. In order to expedite prosecution of the instant application, Applicants have amended claim 1 to recite specific steps, thereby rendering the rejection moot as to the claim. Applicants respectfully request that the rejection be withdrawn.

**Rejections under 35 U.S.C. §103**

Claims 1, 2, 5 and 8-13 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Nurminskaya et al. (hereinafter "Nurminskaya"), in view Hashimoto et al.,(hereinafter "Hashimoto"). Applicants respectfully traverse the rejection as it applies to the pending claims.

The Office maintains that Nurminskaya teaches that expression of transglutaminase (tTGase) and zymogen factor (FXIIIa) is unregulated in chondrocytes. The Office Action further alleges that this disregulation would have been obvious to lead one skilled in the art to the conclusion that blocking activation or activity of these factors would decrease apoptosis "in pathological states", although the Office concedes the reference does no specifically teach as such.

Applicants respectfully submit that there is no common sense or foreseeable justification for the skilled artisan, on reading Nurminskaya in light of Hashimoto, to ascertain that inhibiting transglutaminase (tTGase) and zymogen factor (FXIIIa) would result in effectively treating a pathological calcification in cartilage.

To the contrary, Nurminskaya detracts from the present invention in that the author's emphasis for the study of transglutaminase is focused on *plasma* transglutaminase and not tissue transglutaminase (tTGase). Applicants respectfully direct the Examiner's attention to page 1136, left side column, last paragraph, wherein the authors state:

> "The expression of two transglutaminases in hypertrophic chondrocytes- the *tissue form* (i.e., tTGase) that is constitutively active, and the plasma form that requires proteolytic activation-suggests that each may serve different roles. In the present study, we have

> begun to elucidate these functions in the avian growth cartilage, with emphasis on the enzymatically activated form (i.e., plasma transglutaminase) of factor XIIIA.

Applicants respectfully submit that the author's research focus is clearly directed at study of XIIIA and not at examining the significance of tTGase inhibition. More importantly, the authors clearly suggest that the role of tissue transglutaminase activation with regard to apoptotic cell death is of such little consequence that research efforts in this study were directed away from examination of this form of transglutaminase. The level of unpredictability in the art in this area is such that the skilled artisan could not ascertain that inhibition of tTGase and zymogen factor XIIIA are relevant to any extent in decreasing matrix calcification. Applicants further direct the Examiner's attention to the following from page 1141, second column, first paragraph under "Discussion":

> "we also have observed the mRNA for this form (i.e., tissue transglutaminase) of the enzyme to be upregulated in the hypertrophic zone of the avian growth region. Compared with the plasma form, however, this represents a small portion of overall transglutaminase activity produced by hypertrophic chondrocytes."

Applicants respectfully assert that the reference provides no common sense justification or reasonable foreseeability for the present invention in that the 1) research emphasis in this reference is focused solely at the role of *plasma* XIIIa in cellular apoptosis; 2) the role of tissue transglutaminase is so de-emphasized by the author's data that one skilled in the art would believe only *plasma* XIIIa to be critical in inhibiting cellular apoptosis, not tTGase; and 3) the overall lack of discussion regarding inhibition of activation of FXIIIa and tTGase. It is also noted that focus of the Nurminskaya reference is directed at examination of cellular apoptosis, not as in the present invention, suppressing meniscal and articular cartilage matrix.

Applicants submit that the disclosure of Hashimoto fail to cure the above-described deficiencies in Nurminskaya and do not provide a reasonable foreseeability that the skilled artisan would arrive at the claimed invention. Hashimoto allegedly discloses that articular cartilage matrix

calcification and also that "future treatment options" (e.g., apoptotic inhibitors) would alleviate chondrocyte apoptosis. Applicants respectfully submit that the data presented in Hashimoto merely provides a generalized observation that increased chondrocyte apoptosis occurs in osteoarthritis cartilage and is correlated with the severity of cartilage degradation. Furthermore, Hashimoto is absolutely silent in suggesting any impact of inhibiting zymogen factor FXIIIa or tTGase in preventing such pathology.

Applicants respectfully submit that one of ordinary skill in the art at the time the invention was made would not have found it prima facia obvious to combine the disclosures of Nurminskaya and Hashimoto to arrive at the Applicant's invention. Even if one were motivated to combine the two references, Applicants submit that the proposed combination would not be reasonably foreseeable to a skilled artisan in inhibiting tissue transglutaminase as well as zymogen factor XIIIa. Accordingly, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 3, 4 and 6 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nurminskaya et al., in view of Hashimoto et al., and further in view of Heyninck et al., (herein after "Heyninck"). Applicants respectfully traverse the rejection as it applies to the pending claims. The remarks above distinguishing the invention over the disclosures of Nurminskaya and Hashimoto apply equally here. Heyninck allegedly teaches that cellular expression of A20 inhibits TRAF2 mediated NF-kB signal transduction. Applicants respectfully submit that claim 4 has been cancelled and as such the rejection as it applies to this claim is moot.

With regard to claims 3 and 6, Applicants respectfully submit that although Heyninck discloses data related to the inhibitory impact of A20 on TRAF2, among other factors, the reference is absolutely silent with regard to efficacy of inhibiting the activation of tTGase and FXIIIa. Applicants submit that Heyninck, at most, suggests that inhibition of NFkB signal transduction would yield an anti-apoptotic function for NFkB activation. The focus of this

reference is directed on the finding that there is positive correlation between inhibition of expression of TRADD, RIP, and TRAF2 and expression of A20.

As previously discussed, decreased apoptosis cannot be reasonably held to lead one of ordinary skill in the art to arrive at the Applicant's invention. The expanse of pathological states related to cellular apoptosis and unpredictability in the art is such that it is entirely unreasonable for the Office to hold that inhibiting apoptosis would obviously lead one to determine that inhibition of transglutaminase (tTGase) and zymogen factor (FXIIIa) would result in suppression of calcification in meniscal and articular cartilage matrix.

Applicants submit that the proposed combination would not yield the claimed invention because the inhibition of claim 3 is directly at inhibiting both tTGase as well as FXIIIa, not in inhibiting NFkB signal transduction as in Heyninck. Further, with regard to claim 6, the Heyninck reference discloses that inhibition of IL-1, etc., would result in decreased signal transduction of NFkB, not inhibition of tTGase and FXIIIa as in the claimed invention. Accordingly, there is no reasonable foreseeability, and thus no common sense justification for a skilled artisan to combine the disclosure of Nurminskaya with Hashimoto and Heyninck to arrive at the claimed invention.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 15 under 35 U.S.C. §103(a ) as allegedly being unpatentable over Nurminskaya et al., in view of Hashimoto et al., and further in view of Studer et al (herein after "Studer"). Applicants traverse the rejection as it applies to the pending claim. The remarks above distinguishing the invention over the disclosures of Nurminskaya and Hashimoto apply equally here. Studer allegedly discloses that inhibitors of NOS relieve the inhibition of cartilage matrix synthesis occurring in response to IL-1. The Office also alleges that Studer teaches that NO induces apoptosis in articular chondrocytes leading to eventual calcification in human osteoarthritis. Applicants respectfully submit that the

Examiner has mistakenly referred to the findings in Studer (see page 1632, column 2, last paragraph) in place of those of reference number 12 of Studer (Blanco et al., Am. J. Patho, 1995; 146: 75-85) wherein, Blanco, not Studer, discloses that cells in cartilage are known to produce several mediators that have the potential to induce chondrocyte death through apoptosis or necrosis and among these mediators are cytokines such as IL-1, TNF, IL-17, Fas ligand, oxygen radicals, and *nitric oxide*. Applicants respectfully assert that contrary to the Examiner's conclusion regarding the reference, Studer does not teach that NO induces apoptosis in articular chondrocytes but rather teaches:

> "we have recently transduced chondrocytes with iNOS (NOS-2) gene and confirmed the ability of the endogenously produced NO to inhibit matrix synthesis. Despite the high levels of NO made by these cells, there was <u>no</u> evidence of apoptosis or other forms of cell death." (see Summary, page 377).

The author's findings clearly provide no reasonable foreseeability that the skilled artisan would arrive at the present invention since the available data indicates that despite high levels of NO, apoptosis was *not* observed in iNOS transduced chondrocytes. Hence, given the high level of unpredictability, it cannot be reasonably concluded that a NOS inhibitor as in claim 15 would be contemplated by one of ordinary skill in the art to lie within the realm of reasonable success in inhibiting activation of tTGase and FXIIIa. As previously discussed, decreased apoptosis, in and of itself, cannot be reasonably held to lead one of ordinary skill in the art to arrive at the Applicant's invention.

To the contrary, the findings of Studer, dispute the occurrence of apoptosis in chondrocytes despite a supraphysiological levels of NO. (see Summary, page 377, also see page 378, first column). This conflict in data between Studer and Blanco only serve to underscore the high level of unpredictability in the art and non-obviousness nature of the present invention. Significantly, the references are entirely silent with regard to the observed efficacy of the present invention in inhibiting tTGase and FXIIIa.

Applicants respectfully submit that, like Nurminskaya, Studer, fails to provide a reasonable justification for a common sense combination of the references to deduce that a lack of cellular apoptosis in response to inhibition of NOS would result in inhibition of activation of tTGase and FXIIIa. Accordingly, there can be no foreseeable expectation of successfully combining the disclosure of Nurminskaya with Hashimoto and Studer to arrive at the claimed invention.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection

Applicants respectfully traverse the rejection of claim 2 under 35 U.S.C. §103(a ) as allegedly being unpatentable over Nurminskaya et al., in view of Hashimoto et al., and further in view of Gohr et al (herein after "Gohr"). Applicants respectfully traverse the rejection as it applies to the pending claim. The remarks above distinguishing the invention over the disclosures of Nurminskaya and Hashimoto apply equally here. Applicants respectfully submit that claim 2 has been cancelled and as such the rejection is moot. Withdrawal of the rejection is respectfully requested.

**Conclusion**

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

A check in the amount of $60.00 is enclosed as payment for the one-month Extension of Time Fee. No other fees are deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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